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EXAMINER	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/031,364	Applicant(s) LOCK ET AL.	
	Examiner ALEX NOGUEROLA	Art Unit 1795	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on 01/18/2008 (appeal brief).

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-31 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-31 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Reopening of Prosecution after Appeal

1. In view of the appeal brief filed on January 18, 2008, PROSECUTION IS HEREBY REOPENED. New grounds of rejection are set forth below.

To avoid abandonment of the application, appellant must exercise one of the following two options:

(1) file a reply under 37 CFR 1.111 (if this Office action is non-final) or a reply under 37 CFR 1.113 (if this Office action is final); or,

(2) initiate a new appeal by filing a notice of appeal under 37 CFR 41.31 followed by an appeal brief under 37 CFR 41.37. The previously paid notice of appeal fee and appeal brief fee can be applied to the new appeal. If, however, the appeal fees set forth in 37 CFR 41.20 have been increased since they were previously paid, then appellant must pay the difference between the increased fees and the amount previously paid.

A Supervisory Patent Examiner (SPE) has approved of reopening prosecution by signing below:

/Susy N Tsang-Foster/

Supervisory Patent Examiner, Art Unit 1795

Status of the Rejections pending since the Office action of July 12, 2006

2. All previous rejections are withdrawn.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claim 21 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 21 requires the second signal to be selected to induce a hydrodynamic fluid movement of the suspension. However, claims 1 and 16 both require the suspension of particles to be in a stationary liquid (Applicants considers this a significant feature of their claims). Thus claim 21 appears to be inconsistent with claims 1 and 16, from which claim 21 depends.

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

7. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

8. Claim 1 is rejected under 35 U.S.C. 103(a) as being unpatentable over Masuda et al. ("Movement of Blood Cells in Liquid by Nonuniform Traveling Field," IEEE Transactions on Industry applications, vol. 24, No. 2, March/April 1988) ("Masuda") in view of Hughes et al. ('Dielectrophoretic forces on particles in travelling electric fields," J. Phys. D. Appl. Phys. 29 (1996) 474-482) ("Hughes").

Addressing claim 1, Masuda discloses a method for determining properties (dielectrophoretic properties) of a particle and manipulating and moving particles comprising steps of applying to a suspension of particles in a stationary fluid a first signal at a first frequency and a plurality of different phases whereby the particles experience a traveling wave dielectrophoretic force and simultaneously applying a second signal at a second frequency. See the abstract and *C. Two-Wave Component Electric Curtain Device*, which begins on page 220, and *D. Two-Electrode System*, on page 221. Note that claim 1 does not require the second frequency to be different from the first frequency.

Masuda does not mention whether the traveling dielctrophoretic force due to the first signal has a real part which is negative and also an imaginary part. However, as shown by Hughes it was known at the time of the invention that the dielectrophoresis force acting on particles in traveling electric fields comprises a real part and an imaginary part, which act independently. Moreover, the real part of the dielectrophoretic field can cause a trapping force, if positive, which attracts particles to the electrodes, or a repelling force, if negative, which levitates the particles above the electrodes. The imaginary part can cause particles to translate that is move horizontally over the

electrodes. See the second paragraph of **1. Introduction**, **2.3 Force calculations**, and **3.2. Dielectrophoretic force**. Thus, since the particles in Masuda were translated over the electrodes one with ordinary skill in the art would expect the real part of the traveling wave force to be negative. In any event, in light of Hughes whether the real part of the traveling wave dielectrophoretic force is negative or positive will depend on the desired effect upon certain particle types, namely to trap the certain particle types close to the electrodes or to levitate them and permit translational motion.

As for the second signal altering the magnitude of the real or imaginary part of the first signal, this would be expected since the second signal has the same period, but different phasing than the first signal. So the summed signals should have a magnitude altered with respect to the original first signal and second signal.

9. Claims 3-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Masuda et al. (“Movement of Blood Cells in Liquid by Nonuniform Traveling Field,” IEEE Transactions on Industry applications, vol. 24, No. 2, March/April 1988) (“Masuda”) in view of Hughes et al. (‘Dielectrophoretic forces on particles in travelling electric fields,” J. Phys. D. Appl. Phys. 29 (1996) 474-482) (“Hughes”) as applied to claim 1 above, and further in view of Becker et al. WO 97/27933 A1 (“Becker”) and Talary et al. (“Electromanipulation and separation of cells using traveling electric fields,” J. Phys. D. Appl. Phys. 29 (1996) 2198-2203) (“Talary”) .

Addressing claims 3-15, these claims require either the second signal or second frequency to have different effects on one or more the particle types, such as changing the speed of travel of a particle type or having two types of particles move in opposite directions, or claims 3-15 require the second signal to be a static DEP field or a traveling wave dielectrophoretic field or have particular characteristics to the real part or imaginary part. It should be first noted that none of claims 1-15 directly or indirectly indicate the types of particles to be separated. At the time of the invention a very wide array of different particle types were separated by dielectrophoresis. Becker, for example, discloses separating "..inorganic matter, such as minerals, crystals, colloidal, colloidal, conductive, semi conductive or insulating particles and gas bubbles .. biological matter, such as cells, cell organelles, cell aggregates, nucleic acids, bacterium, protozoans, or viruses … a mixture of cell types, such as fetal nucleated red blood cells in a mixture of maternal blood, cancer cells such as breast cancer cells …" See page 4, lines 12-22. Clearly a wide variety of dielectrophoresis signals will be needed to separate these various particle types. That is why Becker states,

> Signals for the methods of the present invention are in the range of about 0 to about 15 volts, and about 0.1 kHz to about 180 MHz, and more preferably between about 0 to about 5 volts, and about 10 kHz to 10 MHz. These frequencies are exemplary only, as the frequency required for matter discrimination is dependent upon the conductivity of for example, the cell suspension medium. Further, the desired frequency is dependent upon the characteristics of the matter to be discriminated. The discrimination obtained depends on the shape, size and configuration of the electrode elements, for example. In an exemplary embodiment, the signals are sinusoidal, however it is possible to use any periodic or aperiodic waveform. The electrical signals may be developed in one or more electrical signal generators which may be capable of varying voltage, frequency and phase.
> *See page 12, line 16 – page 13, line 10.*

It is the Examiner's position that from the prior art cited in the rejection of claim 1 the additional limitations of claims 3-15 are just separation optimizations or ways of effecting a desired separation of particles within the skill of one with ordinary skill in the art and without requiring undue experimentation:

Masuda discloses using superimposed traveling wave dielectrophoreis fields to move particles as desired including translating particles across electrodes while causing them to move in a circular orbit either clockwise or counter-clockwise. See C*. Two-Wave Component Electric Curtain Device*, which begins on page 220, and *D. Two-Electrode System*, on page 221.

Hughes discloses superimposing two traveling wave dielectrophoresis fields of different frequencies upon one another. Hughes found that the translation forces corresponding to each signal are generated independently. See **3.3 Electrode geometry and signal manipulation** - *(iii) Variation of applied voltage signals* on page 480.

Figure 5 in Talary, for example, discloses that for a sample containing viable and non-viable yeast cells exposed to a signal in a frequency range or window identified as f_1, "the viable cells should exhibit traveling wave dielectrophoresis, with the non-viable ones remaining trapped at the electrodes" and with instead a signal in a frequency window identified as f_2 "the non-viable yeast should exhibit a relatively weak traveling wave motion in the opposite direction to the viable cells at f_1." Thus, Tatary discloses at least having one particle type travel while another particle type does not travel and having two particle types travel in opposite directions. Talary also states,

> As will be described here, through careful control of the conductivity of the suspending medium and the frequency of the applied traveling electric field, viable and non-viable yeast cells could be selectively separated from each other in a mixed suspension and then extracted along the channel in the micro-electrode structure without the application of fluid flow. The direction in which the cells traveled along the channel was determined by their viability and also by the direction of the imposed traveling electric field. To achieve selective cell separation, different experimental conditions were required upon whether the viable or the non-viable cells were to be directed along the channel.
> *See the first paragraph of **3. Results and discussion**, which begins on page 2199*

10. Claims 23-25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Masuda et al. (“Movement of Blood Cells in Liquid by Nonuniform Traveling Field,” IEEE Transactions on Industry applications, vol. 24, No. 2, March/April 1988) (“Masuda”) in view of Hughes et al. (‘Dielectrophoretic forces on particles in travelling electric fields,” J. Phys. D. Appl. Phys. 29 (1996) 474-482) (“Hughes”), Pethig et al.
US 5,795,457 (“Pethig II”), Becker et al. WO 97/27933 A1 (“Becker”), and Pethig et al. WO 97/34689 A1 (“Pethig I”).

Addressing claim 23, Masuda discloses an apparatus for applying a traveling wave dielectrophoresis comprising a dielectrophoresis cell for receiving a fixed quantity of a stationary suspension for particles in a liquid, an electrode array on a substrate forming a wall of the cell and first frequency signal generating means to provide a traveling wave dieletrophoresis force. See the abstract and *C. Two-Wave Component Electric Curtain Device*, which begins on page 220, and *D. Two-Electrode System*, on page 221. Although Masuda does not mention a second signal generating means to

provide a stationary dielectrophoretic force, it should be noted that Masuda does discloses superimposing a second diectrophoresis force. This second force is applied through circuitry designed to cause a phase shift of the first signal.

Hughes discloses superimposing two traveling wave dielectrophoresis fields of different frequencies upon one another. Hughes found that the translation forces corresponding to each signal are generated independently. See **3.3 Electrode geometry and signal manipulation** - *(iii) Variation of applied voltage signals* on page 480.

Becker discloses providing multiple signal generators for applying traveling wave dielectrophoresis and conventional dielectrophoretic fields as desired, albeit in a device in which fluid is non-stationary. See page 11, line 14 – page 13, line 10.

Pethig I disclose superimposing a dielectrophoresis force on apparently two different traveling wave dielectrophoresis forces. See page 12, line 24 – page 13, lne 12.

Pethig II shows that it was known at the time of the invention to superimpose dielectrophoresis fields to enhance separation of particles states that by superimposing a second signal on a first signal "and by an appropriate choice of signal characteristics (i.e. waveform, magnitude and *frequency*) as well as the suspending medium characteristics … particle types 4 and 9 may be separated from each other. [emphasis added]" See col. 04:42-54.

Thus, in light of Hughes, Becker, Pethig I, and Pethig II it would have been obvious to one with ordinary skill in the art at the time of the invention to provide a

second signal generating means so that the second signal can be altered to a greater extent than just by phase shifting as done by the circuitry in Masuda so that the separation of the particle types can be optimized.

Addressing claim 24, since the cited prior art in the rejections of claim 23 already discloses applying two signal generators for enhancing separation of particles, one with ordinary skill in the art at the time of the invention would expect that including a third signal generator would offer even greater separation enhancement.

Addressing claim 25, for the additional initiations of this claim note that in Masuda the electrodes are sandwiched between two microscope slides and the motion of cells was observed through a microscope. See **V. Experimental Apparatus on page 219.**

11. Claim 16 is rejected under 35 U.S.C. 103(a) as being unpatentable over Masuda et al. ("Movement of Blood Cells in Liquid by Nonuniform Traveling Field," IEEE Transactions on Industry applications, vol. 24, No. 2, March/April 1988) ("Masuda") in view of Talary et al. ("Electromanipulation and separation of cells using traveling electric fields," J. Phys. D. Appl. Phys. 29 (1996) 2198-2203) ("Talary") and Pethig et al.

US 5,795,457 ("Pethig II").

Addressing claim 16, Masuda discloses a method for determining properties (dielectrophoretic properties) of a particle and manipulating and moving biological cells, such as erythrocytes, comprising steps of applying to a suspension of biological cells in a stationary fluid a first signal at a first frequency and a plurality of different phases whereby the biological cells experience a traveling wave dielectrophoretic force and simultaneously applying a second signal at a second frequency. Using superimposed traveling wave dielectrophoresis fields Masuda can move the biological cells as desired including translating particles across electrodes while causing them to move in a circular orbit either clockwise or counter-clockwise. See the abstract and *C. Two-Wave Component Electric Curtain Device*, which begins on page 220, and *D. Two-Electrode System*, on page 221. Note that claim 16 does not require the second frequency to be different from the first frequency. Although Masuda does not describe separating unwanted particles from the body fluid particles Masuda does mention that the method was inspired by the need for the ability to separate viable cells from a mixture with minimum damage to the cells, such as separating viable blood cells out of a mixture of microorganisms. See the first paragraph of **1. Introduction** and **VII. Conclusion**.

Talary discloses that traveling wave dielectrophoresis signals at different frequencies will have different effects on biological particles. For example, for a sample containing viable and non-viable yeast cells exposed to a signal in a frequency range or window identified as f_1, "the viable cells should exhibit traveling wave dielectrophoresis, with the non-viable ones remaining trapped at the electrodes" and with instead a signal

in a frequency window identified as f_2 “the non-viable yeast should exhibit a relatively weak traveling wave motion in the opposite direction to the viable cells at f_1.” See Figure 5.

Pethig II, shows that it was known at the time of the invention to superimpose dielectrophoresis fields to enhance separation of particles states that by superimposing a second signal on a first signal "and by an appropriate choice of signal characteristics (i.e. waveform, magnitude and *frequency*) as well as the suspending medium characteristics … particle types 4 and 9 may be separated from each other. [emphasis added]” See col. 04:42-54. In one embodiment Pethig II uses two superimposed dielectrophoresis signals with different frequencies to separate live yeast cells from dead yeast cells. See Example 4 in column 7.

Thus, it would have been obvious to one with ordinary skill in the art at the time of the invention to use the method of Masuda to separate unwanted particles from body fluids because the Masuda article itself states that this is a desirable goal and implies that this goal is the motivation for the development of the disclosed method and because as shown by Talary and Pethig II it was known at the time of the invention to use dielectrophoresis fields to separate unwanted particles from biological particles.

12. Claims 17-20 and 22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Masuda et al. (“Movement of Blood Cells in Liquid by Nonuniform Traveling Field,”

IEEE Transactions on Industry applications, vol. 24, No. 2, March/April 1988) ("Masuda") in view of Talary et al. ("Electromanipulation and separation of cells using traveling electric fields," J. Phys. D. Appl. Phys. 29 (1996) 2198-2203 ("Talary") and Pethig et al. US 5,795,457 ("Pethig II") as applied to claim 16 above, and further in view of .

Addressing claims 17-20 and 22, these claims specify that certain types of cells should be separated from each other, such as blood cells from bacteria, and in a certain way, such as having the bacteria travel while the red blood cells do not travel or with certain a signal frequency or frequency range. As noted in the rejection of claim 16, Masuda discloses the desirability of being able to separate viable cells, such as blood cells, from unwanted cells, such as microorganisms.

Becker, which teaches using combined conventional dielectrophoretic and traveling wave dielectrophoresis to separate cells, albeit with flowing fluid, broadly discloses separating "..inorganic matter, such as minerals, crystals, colloidal, colloidal conductive, semi conductive or insulating particles and gas bubbles .. biological matter, such as cells, cell organelles, cell aggregates, nucleic acids, bacterium, protozoans, or viruses … a mixture of cell types, such as fetal nucleated red blood cells in a mixture of maternal blood, cancer cells such as breast cancer cells in a mixture with normal cells, or red blood cells infested with malarial parasites …" See page 4, lines 12-22. That is why Becker states,

> Signals for the methods of the present invention are in the range of about 0 to about 15 volts, and about 0.1 kHz to about 180 MHz, and more preferably between about 0 to about 5 volts, and about 10 kHz to 10 MHz. These frequencies are exemplary only, as the frequency required for matter

> discrimination is dependent upon the conductivity of for example, the cell suspension medium. Further, the desired frequency is dependent upon the characteristics of the matter to be discriminated. The discrimination obtained depends on the shape, size and configuration of the electrode elements, for example. In an exemplary embodiment, the signals are sinusoidal, however it is possible to use any periodic or aperiodic waveform. The electrical signals may be developed in one or more electrical signal generators which may be capable of varying voltage, frequency and phase.
> *See page 12, line 16 – page 13, line 10.*

Thus, barring a contrary showing, in light of Masuda, which discloses the desirability of separating body fluid particles from unwanted particles, such as microorganisms and Becker, which shows that at the time of the invention a wide variety of separations of unwanted particles from body fluid particles was contemplated, the separation of bacteria, such as E-coli, from body fluid particles, such as blood cells is obvious. Such a method(s) will enable diagnose and treatment of patients and further research for cures for diseases. How the particles are manipulated, the frequencies used, and the use of additional fields is just a matter of what particles are to be recovered, whether some particles are to be further processed, and the number and type of particles. For example, certain particles of interest may be trapped (caused not to travel) and the other particles washed out from the separation device so that the trapped particles of interest can be recovered or particles of interest can be caused to move toward a collection port or collection means to be recovered for further processing while particles not of interest are trapped at the electrodes for later disposal.

13. Claim 21 is rejected under 35 U.S.C. 103(a) as being unpatentable over Masuda et al. (“Movement of Blood Cells in Liquid by Nonuniform Traveling Field,” IEEE Transactions on Industry applications, vol. 24, No. 2, March/April 1988) (“Masuda”) in view of Hughes et al. (‘Dielectrophoretic forces on particles in travelling electric fields,” J. Phys. D. Appl. Phys. 29 (1996) 474-482) (“Hughes”) as applied to claim 1 above and Masuda et al. (“Movement of Blood Cells in Liquid by Nonuniform Traveling Field,” IEEE Transactions on Industry applications, vol. 24, No. 2, March/April 1988) (“Masuda”) in view of Talary et al. (“Electromanipulation and separation of cells using traveling electric fields,” J. Phys. D. Appl. Phys. 29 (1996) 2198-2203 (“Talary”) and Pethig et al. US 5,795,457 (“Pethig II”) as applied to claim 16 above, and further in view of Fuhr et al. (“Travelling wave-driven microfabricated electrohydrodynamic pumps for liquids,” J. Micromech. Microeng. 4 (1994) 217-226) (“Fuhr”).

The references applied to reject claims 1 and 16 do not disclose providing a signal to induce hydrodynamic fluid movement of a suspension. However, as shown by Fuhr it was known at the time of the invention that at sufficient particle densities the whole fluid region containing suspended particles will move upon application of a traveling wave dielectrophoresis field. See **2.2 Fluid pumping induced by suspended microparticels** on page 218. Additionally, the mechanism for inducing traveling-wave pumping was described in detail along with how to manufacture such a pumping means. See the Fuhr article, especially sections 4-8. Thus, barring a contrary showing, such as unexpected results, in light of Fuhr to induce hydrodynamic flow of the suspension is just a matter of how the particle types are to be separated apart. It may be useful, for

example, to keep certain biological particles within a certain fluid suspension medium in order to keep the particles viable. Also, one with ordinary skill in the art at the time of the invention would recognize that the device of Fuhr could also be configured to apply simultaneous dielectrophoresis fields as taught by Masuda with undue effort.

14. Claim 2 is rejected under 35 U.S.C. 103(a) as being unpatentable over Masuda et al. (“Movement of Blood Cells in Liquid by Nonuniform Traveling Field,” IEEE Transactions on Industry applications, vol. 24, No. 2, March/April 1988) (“Masuda”) in view of Hughes et al. (‘Dielectrophoretic forces on particles in travelling electric fields,” J. Phys. D. Appl. Phys. 29 (1996) 474-482) (“Hughes”) as applied to claim 1 above, and further in view of Talary et al. (“Electromanipulation and separation of cells using traveling electric fields,” J. Phys. D. Appl. Phys. 29 (1996) 2198-2203 (“Talary”) and Pethig et al. US 5,795,457 (“Pethig II”).

Although Masuda as modified by Hughes discloses a traveling wave dielectrophoretic force of which there is a real part which is negative and of which there is also an imaginary part (see the rejection of claim 1 above), Masuda as modified by Hughes does not mention whether the application of the second signal causes the frequency range of the window to vary in width.

Talary discloses a method for determining properties (dielectrophoretic properties) of a particle and separating particles comprising steps of applying to a suspension of particles in a stationary fluid a first signal at a first frequency and a plurality of different phases whereby the particles experience a traveling wave dielectrophoretic force of which there is a real part which is negative and of which there is also an imaginary part. See the abstract; Figures 2 and 4; the first full paragraph in the second column on page 2199; and Figure 5 in which the frequency range f_1, which has a negative real part, should be considered. Talary discloses traveling wave dielectrophoresis windows f_1 and f_2 each having a real part which is negative and also an imaginary part. See Figure 5 and the discussion on page 2202 after equation (4). As discussed in the rejection of claim 1 the second signal will be chosen to optimize separation of particles, so it would be expected to differ from the first signal in at least frequency as Figure 5 in Talary shows that different frequency windows have different separation effects. It would also be expected that for a complicated mixture including several different types of particles to separated from each other that frequencies from two or more frequency windows would be needed to separate these several different types of particles. Pethig II, which was cited in the rejection of claim 1 to show that it was known at the time of the invention to superimpose dielectrophoresis fields to enhance separation of particles states that by superimposing a second signal on a first signal "and by an appropriate choice of signal characteristics (i.e. waveform, magnitude and *frequency*) as well as the suspending medium characteristics … particle types 4 and 9 may be separated from each other. [emphasis added]" See col. 04:42-54. Thus,

whether the frequency range of the window is altered will just depend on which particle types are to be separated and how they are to be separated (e.g., trapped or levitated and caused to translate at a different speed than some other particles types).

15. Claims 1-15 and 27-31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Talary et al. ("Electromanipulation and separation of cells using traveling electric fields," J. Phys. D. Appl. Phys. 29 (1996) 2198-2203 ("Talary") in view of Pethig et al. WO 97/34689 A1 ("Pethig I"), Becker et al. WO 97/27933 A1 ("Becker"), Pethig et al. US 5,795,457 ("Pethig II"), and Hughes et al. ('Dielectrophoretic forces on particles in travelling electric fields," J. Phys. D. Appl. Phys. 29 (1996) 474-482) ("Hughes").

Addressing claims 1 and 27, Talary discloses a method for determining properties (dielectrophoretic properties) of a particle and separating particles comprising steps of applying to a suspension of particles in a stationary fluid a first signal at a first frequency and a plurality of different phases whereby the particles experience a traveling wave dielectrophoretic force of which there is a real part which is negative and of which there is also an imaginary part. See the abstract; Figures 2 and 4; the first full paragraph in the second column on page 2199; and Figure 5 in which the frequency

range f_1, which has a negative real part, should be considered. Note that the body of the claim does not include a step of exposing the particle to a chemical or physical agent and a step for determining a response to such exposure, thus these preamble limitations are just intended uses of the claimed method that do not further limit the claim. Also, in any event Talary mentions "… controlled interactions with chemically activated microbeads." See **4. Conclusions** on page 2203.

Talary does not specifically mention "… simultaneously applying a second signal at a second frequency whereby either the real part or the imaginary part of the traveling wave dielectrophoretic force on the particles at the first frequency is altered in magnitude. " However, Talary does disclose that signals at different frequencies will have different effects on the particles. For example, for a sample containing viable and non-viable yeast cells exposed to a signal in a frequency range or window identified as $f_{1,}$ "the viable cells should exhibit traveling wave dielectrophoresis, with the non-viable ones remaining trapped at the electrodes" and with instead a signal in a frequency window identified as f_2 "the non-viable yeast should exhibit a relatively weak traveling wave motion in the opposite direction to the viable cells at f_1." See Figure 5.

Hughes discloses superimposing two traveling wave dielectrophoresis fields of different frequencies upon one another. Hughes found that the translation forces corresponding to each signal are generated independently. See **3.3 Electrode geometry and signal manipulation** - *(iii) Variation of applied voltage signals* on page 480.

Becker discloses simultaneously applying a traveling wave dielectrophoresis signal and a separate conventional dielectrophoresis signal to particles to enhance separation. See page 10, line 08 – page 13, line 10; page 16, lines 1-10; and page 35, lines 14-22.

It would have been obvious to one with ordinary skill in the art at the time of the invention to simultaneously apply a second signal as taught by Hughes and Becker in the invention of Talary because as taught by Becker this will enhance the separation of particles of interest and is consistent with Talary, which, as discussed above, discloses applying different signals, such as f_1 and f_2 having traveling wave dielectrophoeresis and conventional dielectrophoresis aspects for different separation effects. Although Becker discloses non-stationary fluid, the enhanced separation from simultaneously applying the first signal and second signal is not dependent on the fluid flow, but further improved by flowing fluid. The enhanced separation effect is predicted by generalized dielectrophoresis as discussed by Becker (pages 8-13 and page 45, lines 6-12) independently of flowing the fluid. Moreover, as shown by Pethig I and Pethig II it was known at the time of the invention to superimpose dielectrophoresis fields to enhance the separation of particles in a non-stationary fluid. See in Pehtig I the abstract and page 12, line 24 – page 13, line 12 and in Pethig II the abstract; col. 04:14-27;

col. 04:42-64; col. 07:25-63; and claim 1.

It should be noted that if a conventional dielectrophoresis signal is superimposed on the traveling wave signal it, such as taught by Becker, will alter at least the real part

of the traveling wave signal as the conventional dielectrophoresis force "is dependent on the magnitude of the spatial inhomogeneity of the electric field and the in-phase (real) part of the electrical polarization induced in matter by the field." See page 8, lines 18-20 Also, Talary and Becker discuss how the real and imaginary parts of the dielectrophoresis signals will affect discrimination or displacement of particles. See in Talary the second column on page 2201 – the first column on page 2202 and in Becker the first full paragraph on page 12 and the first full paragraph on page 11. Thus, barring a contrary showing the choice of whether to have the second signal alter the magnitude of the real or the imaginary part for the traveling wave dielectrophoresis force (first signal) is just a matter of optimizing the signals to separate out the particles of interest.

For claim 27, note again that Talary discloses a frequency, f_2, at whiff two types of particles are caused to travel in opposite directions. See Figure 5.

Addressing claim 2, Talary discloses traveling wave dielectrophoresis windows f_1 and f_2 each having a real part which is negative and also an imaginary part. See Figure 5 and the discussion on page 2202 after equation (4). As discussed in the rejection of claim 1 the second signal will be chosen to optimize separation of particles, so it would be expected to differ from the first signal in at least frequency as Figure 5 in Talary shows that different frequency windows have different separation effects. It would also

be expected that for a complicated mixture including several different types of particles to separated from each other that frequencies from two or more frequency windows would be needed to separate these several different types of particles. Pethig II, which was cited in the rejection of claim 1 to show that it was known at the time of the invention to superimpose dielectrophoresis fields to enhance separation of particles states that by superimposing a second signal on a first signal "and by an appropriate choice of signal characteristics (i.e. waveform, magnitude and *<u>frequency</u>*) as well as the suspending medium characteristics ... particle types 4 and 9 may be separated from each other. [emphasis added]" See col. 04:42-54. Thus, whether the frequency range of the window is altered will just depend on which particle types are to be separated and how they are to be separated (e.g., trapped or levitated and caused to translate at a different speed than some other particles types).

Addressing claims 3-15 and 28-31, these claims require either the second signal or second frequency to have different effects on one or more the particle types, such as changing the speed of travel of a particle type or having two types of particles move in opposite directions, or claims 2-15 require the second signal to be a static DEP field or a traveling wave dielectrophoretic field or have particular characteristics to the real part or imaginary part. It should be first noted that none of claims 1-15 directly or indirectly

indicate the types of particles to be separated. At the time of the invention a very wide array of different particle types were separated by dielectrophoresis. Becker, for example, discloses separating "..inorganic matter, such as minerals, crystals, colloidal, colloidal, conductive, semi conductive or insulating particles and gas bubbles .. biological matter, such as cells, cell organelles, cell aggregates, nucleic acids, bacterium, protozoans, or viruses … a mixture of cell types, such as fetal nucleated red blood cells in a mixture of maternal blood, cancer cells such as breast cancer cells …" See page 4, lines 12-22. Clearly a wide variety of dielectrophoresis signals will be needed to separate these various particle types. That is why Becker states,

> Signals for the methods of the present invention are in the range of about 0 to about 15 volts, and about 0.1 kHz to about 180 MHz, and more preferably between about 0 to about 5 volts, and about 10 kHz to 10 MHz. These frequencies are exemplary only, as the frequency required for matter discrimination is dependent upon the conductivity of for example, the cell suspension medium. Further, the desired frequency is dependent upon the characteristics of the matter to be discriminated. The discrimination obtained depends on the shape, size and configuration of the electrode elements, for example. In an exemplary embodiment, the signals are sinusoidal, however it is possible to use any periodic or aperiodic waveform. The electrical signals may be developed in one or more electrical signal generators which may be capable of varying voltage, frequency and phase.
> *See page 12, line 16 – page 13, line 10.*

It is the Examiner's position that from the prior art cited in the rejection of claim 1 the additional limitations of claims 3-15 are just separation optimizations or ways of effecting a desired separation of particles within the skill of one with ordinary skill in the art and without requiring undue experimentation. Figure 5 in Talary, for example, discloses that for a sample containing viable and non-viable yeast cells exposed to a signal in a frequency range or window identified as f_1, "the viable cells should exhibit

traveling wave dielectrophoresis, with the non-viable ones remaining trapped at the electrodes" and with instead a signal in a frequency window identified as f_2 "the non-viable yeast should exhibit a relatively weak traveling wave motion in the opposite direction to the viable cells at f_1." Thus, Tatary discloses at least having one particle type travel while another particle type does not travel and having two particle types travel in opposite directions. Talary also states,

> As will be described here, through careful control of the conductivity of the suspending medium and the frequency of the applied traveling electric field, viable and non-viable yeast cells could be selectively separated from each other in a mixed suspension and then extracted along the channel in the micro-electrode structure without the application of fluid flow. The direction in which the cells traveled along the channel was determined by their viability and also by the direction of the imposed traveling electric field. To achieve selective cell separation, different experimental conditions were required upon whether the viable or the non-viable cells were to be directed along the channel.
> *See the first paragraph of* ***3. Results and discussion****, which begins on page 2199*

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to ALEX NOGUEROLA whose telephone number is (571) 272-1343. The examiner can normally be reached on M-F 8:30 - 5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, NAM NGUYEN can be reached on (571) 272-1342. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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/Alex Noguerola/
Primary Examiner, Art Unit 1795